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☐	L6	((N$1modif$ or N$1link$ | N$1methylat$ or N$1alkyl$ or N$1substitut$) and (beta with (strand?| sheet?| structure))) and beta amyloid	272
☐	L5	((N$1modif$ or N$1link$ | N$1methylat$ or N$1alkyl$ or N$1substitut$) and (beta with (strand?| sheet?| structure))) and beta with amyloid	334
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END OF SEARCH HISTORY

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N?substitut?)  and (beta (A) (strand or sheet or structure))
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N(1W)alkyl? or N(1W)substitut?)  (S) (beta (A) (strand or sheet or structure)))
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      RAND OR SHEET OR STRUCTURE)))

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F2          16   DGENE
F3           6   CAPLUS
F4           5   TOXCENTER
F5           4   ESBIOBASE
F6           2   BIOTECHNO
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      STN
ACCESSION NUMBER:         2005191117   ESBIOBASE
TITLE:                    Inhibition of hIAPP amyloid-fibril formation
                          and apoptotic cell death by a designed hIAPP
                          amyloid-core-containing hexapeptide
```

AUTHOR: Tatarek-Nossol M.; Yan L.-M.; Schmauder A.; Tenidis K.; Westermark G.; Kapurniotu A.
CORPORATE SOURCE: A. Kapurniotu, Laboratory of Bioorganic and Medicinal Chemistry, Institute of Biochemistry, University Hospital of the Rheinisch-Westfalische Technische Hochschule Aachen, D-52074 Aachen, Germany. E-mail: akapurniotu@ukaachen.de
SOURCE: Chemistry and Biology, (2005), 12/7 (797-809), 68 reference(s) CODEN: CBOLE2 ISSN: 1074-5521
PUBLISHER ITEM IDENT.: S1074552105001560
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The pathogenesis of type II diabetes is associated with the aggregation of the 37-residue human islet **amyloid** polypeptide (hIAPP) into cytotoxic .**beta**. **sheet** aggregates and fibrils. We have recently shown that introduction of two N-methyl rests in the .**beta**. **sheet**- and **amyloid**-core-containing sequence hIAPP(22-27), or NFGAIL converted this amyloidogenic and cytotoxic sequence into nonamyloidogenic and noncytotoxic NF(N-Me)GA(N-Me)IL. Here, we show that NF(N-Me)GA(N-Me)IL is able to bind with high-affinity full-length hIAPP and to inhibit its fibrillogenesis. NF(N-Me)GA(N-Me)IL also inhibits hIAPP-mediated apoptotic β cell death. By contrast, unmodified NFGAIL does not inhibit hIAPP amyloidogenesis and cytotoxicity, suggesting that **N-methylation** conferred on NFGAIL the properties of NF(N-Me)GA(N-Me)IL. These results support the concept that rational **N-methylation** of hIAPP **amyloid**-core sequences may be a valuable strategy to design pancreatic-**amyloid** diagnostics and therapeutics for type II diabetes. .COPYRGT.2005 Elsevier Ltd All rights reserved.

L15 ANSWER 2 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2005:242252 CAPLUS
DOCUMENT NUMBER: 143:281207
TITLE: Inhibition of IAPP toxicity and aggregation into .**beta**.-**sheets** and **amyloid** by a rationally **N-methylated**, IAPP **amyloid** core-containing hexapeptide
AUTHOR(S): Kapurniotu, A.; Schmauder, A.; Tatarek-Nossol, M.; Tenidis, K.
CORPORATE SOURCE: Laboratory of Medicinal and Bioorganic Chemistry, Institute of Biochemistry, University Hospital of the RWTH Aachen, Aachen, D-52074, Germany
SOURCE: Amyloid and Amyloidosis, [International Symposium on Amyloidosis], 10th, Tours, France, Apr. 18-22, 2004 (2005), Meeting Date 2004, 494-496. Editor(s): Grateau, Gilles; Kyle, Robert A.; Skinner, Martha. CRC Press LLC: Boca Raton, Fla. CODEN: 69GPWW; ISBN: 0-8493-3534-5
DOCUMENT TYPE: Conference
LANGUAGE: English

AB A minimalistic, structure-based chemical strategy was developed to transform **amyloid** core-containing sequences into non-amyloidogenic ones that are able to interact with the native sequences and inhibit **amyloid** formation and cytotoxicity. This was achieved via the rational **N-methylation** of a min. of two amide bonds on the same side of the strand of the .**beta**.-**sheet** of the **amyloid** core region. The applicability of this strategy was demonstrated by using various **amyloid** core-containing sequences of islet **amyloid** polypeptide (IAPP) that have been N-methylated based on a NMR-derived structural model of pancreatic **amyloid**. It was shown that N-methylation at G24 and I26 in short IAPP amyloidogenic and cytotoxic sequences, including the NFGAIL one, is able to convert these sequences into non-amyloidogenic and non-cytotoxic ones. Moreover, the rationally designed analog NF(N-Me)GA(N-Me)IL was shown to be able to interact with full length IAPP and inhibit IAPP **amyloid** formation.

Importantly, NF(N-Me)GA(N-Me)IL was found to be able to reduce the cytotoxic effect of IAPP aggregates on rat insulinoma cells. The results also suggest that these effects are due to the presence of the N-Me conformational constraints within the **amyloid** core region NFGAIL.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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ACCESSION NUMBER: 2004149754 ESBIOBASE
TITLE: Evidence for assembly of prions with left-handed β-helices into trimers
AUTHOR: Govaerts C.; Wille H.; Prusiner S.B.; Cohen F.E.
CORPORATE SOURCE: S.B. Prusiner, HSE-774, 513 Parnassus Avenue, San Francisco, CA 94143-0518, United States.
E-mail: stanley@itsa.ucsf.edu
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (01 JUN 2004), 101/22 (8342-8347), 59 reference(s)
CODEN: PNASA6 ISSN: 0027-8424
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Studies using low-resolution fiber diffraction, electron microscopy, and atomic force microscopy on various **amyloid** fibrils indicate that the misfolded conformers must be modular, compact, and adopt a cross-.**beta**. **structure**. In an earlier study, we used electron crystallography to delineate molecular models of the N-terminally truncated, disease-causing isoform (PrP.sup.S.sup.c) of the prion protein, designated PrP 27-30, which polymerizes into **amyloid** fibrils, but we were unable to choose between a trimeric or hexameric arrangement of right- or left-handed β-helical models. From a study of 119 all-β folds observed in globular proteins, we have now determined that, if PrP .sup.S.sup.c follows a known protein fold, it adopts either a β-sandwich or parallel β-helical architecture. With increasing evidence arguing for a parallel . **beta**.-**sheet** organization in **amyloids**, we contend that the sequence of PrP is compatible with a parallel left-handed β-helical fold. Left-handed β-helices readily form trimers, providing a natural template for a trimeric model of PrP.sup.S.sup.c. This trimeric model accommodates the PrP sequence from residues 89-175 in a β-helical conformation with the C terminus (residues 176-227), retaining the disulfide-linked α-helical conformation observed in the normal cellular isoform. In addition, the proposed model matches the structural constraints of the PrP 27-30 crystals, positioning residues 141-176 and the **N-linked** sugars appropriately. Our parallel left-handed β-helical model provides a coherent framework that is consistent with many structural, biochemical, immunological, and propagation features of prions. Moreover, the parallel left-handed β-helical model for PrP.sup.S.sup.c may provide important clues to the structure of filaments found in some other neurodegenerative diseases.

L15 ANSWER 4 OF 27 IFIPAT COPYRIGHT 2005 IFI on STN

AN 10386064 IFIPAT;IFIUDB;IFICDB
TITLE: INHIBITORS AND DISASSEMBLERS OF FIBRILLOGENESIS; A PEPTIDES FOR TREATING **AMYLOID** FIBRILS; DRUG SCREENING FOR POTENTIAL ANTAGONIST; ANTIFIBRILLATORY AGENTS
INVENTOR(S): Gordon; David J., Chicago, IL, US
Meredith; Stephen C., Chicago, IL, US
PATENT ASSIGNEE(S): Unassigned
PATENT ASSIGNEE PROBABLE: Chicago, University of (Probable)
AGENT: BARNES & THORNBURG, 2600 CHASE PLAZA, 10 LASALLE STREET, CHICAGO, IL, 60603

NUMBER	PK	DATE

PATENT INFORMATION:	US 2003130484	A1	20030710
APPLICATION INFORMATION:	US 2002-103658		20020320

	NUMBER	DATE
PRIORITY APPLN. INFO.:	US 2001-277477P	20010320 (Provisional)
FAMILY INFORMATION:	US 2003130484	20030710
DOCUMENT TYPE:	Utility Patent Application - First Publication	
FILE SEGMENT:	CHEMICAL APPLICATION	

GOVERNMENT INTEREST:

(0002) The government owns rights in the present invention pursuant to grant number T32 GM07281 from the National Institutes of Health. This work was also supported by the Alzheimer's Association Grant IIRG# 98-1344.

PARENT CASE DATA:

This invention claims priority from U.S. Serial No. 60/277,477 filed Mar. 20, 2001 incorporated herein by reference.

NUMBER OF CLAIMS: 11 28 Figure(s).

DESCRIPTION OF FIGURES:

FIG. 1(A) is a diagram of A beta 136-22m; (B) is a diagram of A beta 16-22m(4) that illustrates the position of the methyl groups when the peptides are arrayed in a-strand conformation. In FIG. 1(A) and FIG. 1(B), carbon atoms on amide and amino nitrogen atoms are medium gray; other hydrogen atoms are not shown. In A beta 16-22m or A beta 16-22mR, the methyl groups are aligned on only one face of the **beta strand**. In contrast, the methyl groups are located on both faces of the A beta 1622m(4) peptide.

FIG. 2(A) shows inhibition of fibrillogenesis and (B) disassembly of A beta 40 fibrils by inhibitor and control peptides. In FIG. 2A, A beta 40 samples were incubated for one week at 37 degrees C. in the presence of various concentrations of peptides; thioflavin induced fluorescence was then measured. In FIG. 2(B), the peptide inhibitors were added to A beta 40 fibrils which had been pre-formed by incubating A beta 40 for one week at 37 degrees C. After addition of peptide inhibitors, the mixtures were incubated for an additional three days at 37 degrees C. After incubations, a 5 mu l aliquot of peptide solution was diluted into 1 mil of 50 mm glycine, pH 8.5, containing 5 uM thioflavin. Data are expressed as a percentage of the signal obtained in the absence of inhibitor peptides. Symbols are as follows: (circle-solid) A beta 16-22m; (*) A beta 16-22mR; (Delta) A beta 16-22; (*) A beta 16-22m(4); (x) PrPm; (composite-function) Ac-A beta 16-22.

FIG. 3(A) shows electron microscopic examination of the effect of A beta 16-22m on fibril formation, electron micrographs of A beta 40 fibrils formed after a one week incubation at pH 7.4. Magnification, x 42,000. (B) is an electron micrograph of A beta 40 incubated with A beta 16-22m (30-fold molar excess) for seven days. Magnification, x 17,000.

FIG. 4(A) shows analytical ultracentrifugation sedimentation equilibrium of 100 mu M; (B) 500 mu M; and (C) 5 mM solution of A beta 16-22 min buffer (100 mM phosphate, 15mM NaCl, pH 7.4) at 36,000 rpm, 48,000 rpm and 54,000 rpm. The data are displayed as normalized log plots. A homogeneous sample should exhibit a series of parallel lines with the same slope (MW) for all rotor speeds. The solid lines drawn through the data were obtained by fitting the Ln(Absorbance) versus radius2 data to an equation of a single ideal species. Higher order fits resulted in poorer agreement with the experimental data. The residual differences between the experimental data and theoretical curves are plotted in the side panels.

FIG. 5 shows circular dichroic spectra of inhibitor peptides. (A) compares the spectra of A beta 16-22 and A beta 16-22m. (13) shows examination of the concentration dependence of the over (**beta**))**sheet** structure as reflected by the mean residue ellipticity at 226 nm.

FIG. 6 shows results of protease resistance of A beta 16-22 and A beta 16-22m. Peptides were incubated for 24 h at 37 C with 1% (w/v) chymotrypsin. The percentage of undigested peptide was determined by RC-HPLC as described in the Materials and Methods. The data show chromatographs of A beta 16-22m (A) before and (B) after incubation with chymotrypsin; and of A beta 16-22 (C)

before and (D) after incubation with chymotrypsin. The arrow marks the position of the intact.
FIG. 7 shows the structure of (A) A beta 16-20m, (B) Anth-A beta 16-20m, (C) A beta 16-20, (D) A beta 16-22R, and (E) PrP115122m, all arrayed with a ***beta*** **-strand** conformation. In all of the **N-** ***methylated*** peptides depicted in the figure, the methyl groups would be aligned on one face of a **beta-strand**.
FIG. 8 shows electron microscopic examination of the effect of A beta 16-20 and A beta 16-20m on A beta 1-40 fibril formation. (A) Electron micrograph of A beta 1-40 incubated in the absence of inhibitor. Magnification, x 17,000. (B) Electron micrograph of A beta 1-40 incubated with a 20-fold molar excess of A beta 16-20m for seven days. Magnification, x 45,000. (C) Electron micrograph of A beta 1-40 incubated with a 20-fold molar excess of A beta 16-20 for seven days. Magnification, x 45,000. (D) Electron micrograph of A beta 16-20 added to A beta 1-40 fibrils which had been pre-formed by incubating A beta 1-40 for five days at 37 degrees C. Magnification x 45,000. (E) Electron micrograph of A beta 16-20 incubated in the absence of other peptides. Magnification x 45,000.
FIG. 9 shows inhibition and disassembly of A beta 40 fibrils by inhibitor peptides. (A) A beta 40 samples were incubated for one week at 37 degrees C. in the presence of various concentrations of peptides; thioflavin fluorescence was measured. In FIG. (B), the peptide inhibitors were added to A beta 40 fibrils which had been pre-formed by incubating A beta 40 for one week at 37 degrees C. After addition of peptide inhibitors, the mixtures were incubated for an additional three days at 37 C. After the incubation, a 10 mu l aliquot of peptide solution was diluted into 1 ml of 50 mM glycine, pH 8.5, containing 5 mu M thioflavin. Data are expressed as a percentage of the signal obtained in the absence of inhibitor peptides. The data are fit to an equation for a hyperbola parameters divided from nonlinear least squares analysis. Symbols are as follows: (circle-solid) A beta 16-20m; (*) A beta 16-20; (diamond-suit) AnthA beta 16-20m; (up-trianglefilled) A beta 16-22R.
FIG. 10 shows the rate of A beta 40 fibrils that had been preformed by incubating A beta 40 for one week at 37 degrees C. At the specified time points, a 5 mu l aliquot of each peptide solution was diluted into 1 mil of 50 mM glycine, pH 8.5, containing 5 mu M thioflavin. Data are expressed as a percentage of the signal obtained in the absence of inhibitor peptides. The data are fit to the equation for a first order rate process. Symbols are as follows: (circle-solid)A beta 1620m; A40 molar ratio, 5:1; A beta 16-20m:A beta 40 molar ratio, 10:1; (diamond-suit) A beta 16-20m:A beta 40 molar ratio, 20:1; (up-triangle-filled) A beta 16-20m:A beta beta 40 molar ratio, 30:1; (down-triangle-filled); A beta 16-20m:A beta 40 molar ratio, beta 40:1.
FIG. 11 shows inhibition of fibrillogenesis and disassembly of pre-formed fibrils is sequence specific. A beta 40 or Prp106126 was allowed to form fibrils. Each fibril-forming peptide was tested with A beta 16-20m or Prp115-112m. Extent of fibril formation or fibril disassemble was measured using a thioflavin fluorescence assay, as described herein. The X-axis is the ratio (mol:mol) of inhibitor peptide to fibril forming peptide for the various combinations; the Y-axis is the fluorescence expressed as a percentage of fluorescence obtained in the absence of inhibitor peptide. Lines are designated as representing either fibrillogenesis inhibition, or fibril disassembly. Symbols are as follows: (circle-solid) Prp115122 m+PrP106-126, Inhibition; (*) A beta 16-20 m+PrP106-126, Inhibition; (diamond-suit) A beta 16-20 m+PrP106-126, Disassembly; (up-triangle-filled) PrP115-122 m+A beta 40, Inhibition; (down-triangle-filled) PrP115-122 m+A beta 40, Disassembly.
FIG. 12 shows (A) analytical ultracentrifugation sedimentation equilibrium of a 200 EM solution of A beta 16-20m in buffer (100 mM phosphate, 150 mM NaCl, pH 7.4) at 60,000 rpm. The data are displayed as normalized log plots. The solid lines drawn through the data were obtained by fitting the In (Absorbance) versus radius2 data to an equation of a single ideal species. Higher order fits resulted in poorer agreement with the experimental data. (B) The residual differences between the experimental data and theoretical curves are plotted in. (C) Size exclusion chromatography of an A beta 16-20m (1 mM) sample incubated at 37 degrees C. for one hour and (D) 72 hours. The column buffer was 100 mM phosphate buffer with 150 mM NaCl, pH 7.4. Absorbance was measured at 220 nm. The column volume is indicated by an arrow.
FIG. 13 shows circular dichroic spectra of A beta 16-20 and A beta 16-20m. (A) compares the spectra of A beta 16-20 (lambda) and A beta 16-20m (nu). The effects of (B) peptide concentration, (C) urea and (D) pH on the **beta -sheet** structure of A beta 16-20m, as reflected by the mean residue ellipticity at 226 nm, are displayed in the following panels. Data were

collected as described in the experimental section.
FIG. 14 shows NMR spectroscopy of the A beta 16-20m peptide in phosphate buffer. (A) TOCSY spectra expanded in the H alpha proton region. Spin systems are identified by the single letter amino acid code and residue number. (B) ROESY spectra expanded in the H alpha proton region. Data were collected on a Varian 600 MHz instrument using presaturation for solvent suppression. Peaks were assigned using the TOCSY and DQF-COSY data.

DESCRIPTION OF FIGURES:

FIG. 15 shows (A) efflux of (up-triangle-filled) 14C-A beta 1620m alone, (diamond-suit) 3H-glycine alone, and a mixture of 14C-A beta 16-20m (*) and 3H-glycine (circle-solid) from phosphotidylcholine vesicles. Phosphtidylcholine vesicles were prepared in the presence of 14C-labeled beta 16-20, 3H-glycine or a mixture of the two compounds. Free beta 16-20m and glycine were separated from the vesicles by passage over a G25 column (Pharmacia). The efflux of A beta 16-20m and glycine were measured using an ultrafiltration assay. Flux is expressed as a fraction of the total label; data were fit to a first-order rate equation. Efflux of calcein from phospotidylcholine vesicles. (B) different concentrations of A beta 16-20m (circle-solid) and A beta 16-20 (*) were incubated with phosphotidylcholine vesicles containing calcein for 3 hours at 37 degrees C. The fluorescence of the samples were then measured with an excitation wavelength of 490 nm and an emission wavelength of 520 nm. Data are expressed as a fraction of maximal fluorescence. (C) the rate of calcein efflux from phospotidylcholine vesicles was measured in the presence of beta 400 mu M A beta 16-20m. Fluorescence is expressed in arbitrary units. Data are fit to an equation for a first order rate process. (D) right angle light scattering of a vesicle solution in the presence (*) or absence (circle-solid) of A beta 16-20m. The turbidity of the solutions were measured by following the 90 degrees light scattering on a fluorescence spectrophotometer with both the excitation and emission wavelengths set to 600 nm. (E) and (F) Fluorescence data are expressed as arbitrary units. Fluorescence microscopy of COS cells incubated for twelve hours with 50 mu g of Anth beta 1620m. After the incubation period, the cells were washed, fixed with formaldehyde and examined by fluorescence microscopy using a DAPI filter.
FIG. 16 shows structures of (A) A beta 16-20m, (B) A beta 16-20 m2, (C) Anth-A beta 16-20m, (D) A beta 16-20, (E) A beta 16-20s and (F) PrP115-122m. All peptides are displayed in a betastrand conformation. In the N-methyl peptides shown in the FIG., the methyl groups are aligned on one hydrogen bonding face of the D-strand.
FIG. 17 shows Inhibition and disassembly of A beta 1-40 fibrils by inhibitor peptides. In (A), A beta 1-40 samples were incubated for one week at 37 degrees C. in the presence of various concentrations of inhibitor peptides; Thioflavin T fluorescence was then measured as described in Methods and Materials. In (B), the peptide inhibitors were added to A beta 1-40 fibrils which had been pre-formed by incubating A beta 140 for five days at 37 degrees C. After addition of the peptide inhibitors, the mixtures were incubated for an additional three days at 37 degrees C. and then the Thioflavin T fluorescence of the samples were measured as described in the experimental section. Data are expressed as a percentage of the signal obtained in the absence of inhibitor peptides. The data were fit to an equation for a hyperbola, as described in the Materials and Methods; parameters are derived from nonlinear least squares analysis. Symbols are as follows: (lambda) A beta 16-20m; (nu) A beta 16-20; (upsilon) Anth-A beta 1620m; (sigma) A beta 16-20 m2; (tau)A, 16-20s.
FIG. 18 shows (A) Equilibrium analytical ultracentrifugation of a 1 mM solution of A beta 16-20m in buffer (100 mM phosphate, 150 mM NaCl, pH 7.4) at 36,000 (lambda), 42,000 (nu) and 48, 000 (upsilon) rpm. The data are displayed as normalized log plots. The solid lines drawn through the data were obtained by fitting the In (Absorbance) versus radius2 data to an equation of a single ideal species. Higher order fits resulted in poorer agreement with the experimental data. The residual differences between the experimental data and theoretical curves are plotted in (B).
FIG. 19 shows (A) Efflux of (sigma) 14C-A beta 16-20m alone, (upsilon) 3H-glycine alone, and a mixture of 14C-A beta 16-20m (v) and 3H-glyine (lambda) from phosphatidylcholine vesicles. Phosphatidylcholine vesicles were prepared in the presence of 14C-labeled A beta 16-20m, 3H-glycine or a mixture of the two compounds. Free A beta 16-20m and glycine were separated from the vesicles by passage over a PD-10 Sephadex G25 column (Pharmacia). The efflux of A beta 16-20m and glycine was measured using an ultrafiltration assay described in the Materials and Methods and quantitated with scintillation counting. Efflux is expressed as a fraction of the total. (B) Efflux of calcein from

phosphatidylcholine vesicles. Different concentrations of A beta 16-20m (lambda) and A beta 16-20 (nu) were incubated with phosphatidylcholine vesicles containing calcein for 3 hours at 37 degrees C. The fluorescence of the samples was then measured with an excitation wavelength of 490 nm and an emission wavelength of 520 nm. Data are expressed as a fraction of maximal fluorescence. (C) Right angle light scattering of a vesicle solution in the presence (nu) or absence (lambda) of A beta 16-20m. The turbidity of the solutions was measured by following the 90 degrees light scattering on a fluorescence spectrophotometer with both the excitation and emission wavelengths set to 600 nm. Scattering data are expressed as arbitrary fluorescence units.

FIG. 20 shows (A) Fluorescence microscopy of COS cells incubated for twelve hours with 40 mu M Anth-A beta 16-20m. After the incubation period, the cells were washed, fixed with formaldehyde and examined by fluorescence microscopy using a DAPI filter. (B) HPLC chromatogram of the Anth-A beta 16-20m peptide before incubation with COS cells. The elution gradient was from 0%-60% acetonitrile in 60 minutes. The peptide was detected by measuring the absorbance at 346 nm. (C) HPLC chromatogram of Anth-A beta 16-20m peptide that had been internalized by COS cells and then reisolated, as described in the Materials and Materials. The N-methyl anthranilic acidlabeled peptide was identified in the presence of other cellular peptides and proteins by fluorescence spectroscopy. The excitation and emission wavelengths were 346 nm and 435 nm, respectively. The HPLC gradient is the same as in (A).

FIG. 21 shows that as described above (FIG. 3), A beta 1-40 or Prp106-126 was allowed to form fibrils, as described in Methods, either in the presence of absence of a fibrillogenesis inhibitor. Each fibril-forming peptide was tested with A beta 16-20m or Prp115-122m. Extent of fibril formation or fibril disassembly was measured using a thioflavin fluorescence assay, as described above. In the FIG., the x-axis is the ratio (mol:mol) of inhibitor peptide to fibril forming peptide for the various combinations; the y-axis is the fluorescence expressed as a percentage of fluorescence obtained in the absence of inhibitor peptide. Symbols are as follows: (lambda) PrP115-122 m+PrP106-126, Inhibition; (nu) A beta 16-20 m+PrP106-126, Inhibition; (upsilon) A beta 16-20 m+PrP106-126, Disassembly; (sigma) PrP115-122 m+A beta 1-40, Inhibition; (tau) PrP115-122 m+A beta 1-40, Disassembly. (mu) A beta 1620s+A beta 1-40, Inhibition; (*)A beta 16-20s+A beta 1-40, Disassembly.

FIG. 22 shows inhibition of fibrillogenesis (A) and dissasembly (B) of A beta 40 fibrils by inhibitor and control peptides. Data were collected as described in the experimental section. Data are expressed as a percentage of the signal obtained in the absence of inhibitor peptides. In the figures, points represent experimental data, and the line is a theoretical curve. Data were analyzed on the model of acomplex betweenA beta 40 and the smaller peptides, using the equation:

FIG. 23 shows the concentration dependence of the aggregation is analyzed by ploting fraction of oligomer versus total peptide concentration, using the equation in the text.

FIG. 24 shows how size exclusion chromatographs were obtained using a Superdex Peptide (Pharmacia) column. Peptide concentrations were 0.1, 0.2, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0 mg/ ml, as indicated. Chromatpographs are scaled so that, in each case, the largest peak is full scale. The data are consistent with the proposal that the ppetides undergo a reversible monomer-oligomer equilibrium. Both peaks eluted after the inclusion volume of the column as determined by the elution time of acetic acid and other low molecular weight markers). Although the recovery of the peptide from the column was virtually quantitative, the late elution of the peptides was consistent with adsorption of the peptide on all of the columns. For this reason, it was not possible to determine a molecular weight of the oligomer by this technique. Nevertheless, the concentration dependency of the aggregation could be analyzed using the following inferences. First, because the relative proportion of peptide in the earlier eluting peak increased with increasing concentration, we inferred that the earlier eluting peak was the oligomer. Second, since no other peaks were ever observed in any of the chromatograms, we inferred that the equilibrium could be analyzed as a simple case involving only two species. Third, because no peptide was observed to elute between the two peaks, and there was no "tailing" or either peak, we inferred that the equilibration was sufficiently slow that significant re-equilibration did not occur within the time frame of the chromatography. Using these inferences, the monomer-oligomer equilibrium was analyzed as described in the text.

FIG. 25 shows the mean residue ellipticity of A beta 16-22m and A beta 16-22mR

were independent of peptide concentration. The graph shows the mean residue ellipticity at 226 nm as a function of total peptide concentration.

DESCRIPTION OF FIGURES:

FIG. 26 shows structures of A beta 16-20 (A), A beta 16-20e (B) A beta 16-20m (C) PrP117-121 e (D) and (E) A beta 16-20-Bpa drawn with the peptide in beta-strand conformationss. In the ester and N-methyl peptides, the backbone modifications at alternating residues are aligned on one hydrogen bonding face of the beta-strand.

FIG. 27 ESI-MS detects non-covalent dimers of the A beta peptides. Shown are ESI-MS spectra of 250 mu M solutions of A beta 16-20e (A), A beta 16-20 (B) and A beta 16-20m (C). The samples were prepared in deionized water and the data were collected as described in the Materials and Methods section. The peaks corresponding to the monomer and dimer molecular weights for each peptide are labeled on the spectra.

FIG. 28 shows A beta 16-20-Bpa forms a covalent dimer upon irradiation with UV light. The MADI-MS spectrum of a 500 mu M solution of A beta 16-20 Bpa irradiated for 30 min at 350 nm shows peaks at 801.1 Da and 1600.8 Da, corresponding to monomeric and dimeric A 16-20-Bpa, respectively. The inset panel demosntrates that in the absence of irradiation, the dimer peak at 1600.8 Da is not observed in the MALDI-MS spectrum. !

AB Methods and compositions are presented that inhibit fibril formation and/or bring about disassembly of pre-formed fibrils. Compositions include peptides with short beta -strands with two faces: one that can bind to beta -**amyloids** through hydrogen bonds, and one which blocks propagation of hydrogen bonding needed to form fibrils. Thus, short congeners of the fibril protein containing N-methyl amino acids or esters are provided for the inhibition of fibril formation and for the disassembly of pre-existing or pre-formed fibrils. Specific aspects address beta -**amyloid** fibrils; prion mediated fibrils; Huntington protein fibrils. Methods for screening for potential fibril inhibitors and disassemblers, diagnostic analysis and treatments are provided.

CLMN 11 28 Figure(s).

FIG. 1(A) is a diagram of A beta 136-22m; (B) is a diagram of A beta 16-22m(4) that illustrates the position of the methyl groups when the peptides are arrayed in a-strand conformation. In FIG. 1(A) and FIG. 1(B), carbon atoms on amide and amino nitrogen atoms are medium gray; other hydrogen atoms are not shown. In A beta 16-22m or A beta 16-22mR, the methyl groups are aligned on only one face of the **beta strand**. In contrast, the methyl groups are located on both faces of the A beta 1622m(4) peptide.

FIG. 2(A) shows inhibition of fibrillogenesis and (B) disassembly of A beta 40 fibrils by inhibitor and control peptides. In FIG. 2A, A beta 40 samples were incubated for one week at 37 degrees C. in the presence of various concentrations of peptides; thioflavin induced fluorescence was then measured. In FIG. 2(B), the peptide inhibitors were added to A beta 40 fibrils which had been pre-formed by incubating A beta 40 for one week at 37 degrees C. After addition of peptide inhibitors, the mixtures were incubated for an additional three days at 37 degrees C. After incubations, a 5 mu l aliquot of peptide solution was diluted into 1 mil of 50 mm glycine, pH 8.5, containing 5 uM thioflavin. Data are expressed as a percentage of the signal obtained in the absence of inhibitor peptides. Symbols are as follows: (circle-solid) A beta 16-22m; (*) A beta 16-22mR; (Delta) A beta 16-22; (*) A beta 16-22m(4); (x) PrPm; (composite-function) Ac-A beta 16-22.

FIG. 3(A) shows electron microscopic examination of the effect of A beta 16-22m on fibril formation, electron micrographs of A beta 40 fibrils formed after a one week incubation at pH 7.4. Magnification, x 42,000. (B) is an electron micrograph of A beta 40 incubated with A beta 16-22m (30-fold molar excess) for seven days. Magnification, x 17,000.

FIG. 4(A) shows analytical ultracentrifugation sedimentation equilibrium of 100 mu M; (B) 500 mu M; and (C) 5 mM solution of A beta 16-22 min buffer (100 mM phosphate, 15mM NaCl, pH 7.4) at 36,000 rpm, 48,000 rpm and 54,000 rpm. The data are displayed as normalized log plots. A homogeneous sample should exhibit a series of parallel lines with the same slope (MW) for all rotor speeds. The solid lines drawn through the data were obtained by fitting the Ln(Absorbance) versus radius2 data to an equation of a single ideal species. Higher order fits resulted in poorer agreement with the experimental data. The residual differences

between the experimental data and theoretical curves are plotted in the side panels.

FIG. 5 shows circular dichroic spectra of inhibitor peptides. (A) compares the spectra of A beta 16-22 and A beta 16-22m. (13) shows examination of the concentration dependence of the over (**beta**))**sheet** structure as reflected by the mean residue ellipticity at 226 nm.

FIG. 6 shows results of protease resistance of A beta 16-22 and A beta 16-22m. Peptides were incubated for 24 h at 37 C with 1% (w/v) chymotrypsin. The percentage of undigested peptide was determined by RC-HPLC as described in the Materials and Methods. The data show chromatographs of A beta 16-22m (A) before and (B) after incubation with chymotrypsin; and of A beta 16-22 (C) before and (D) after incubation with chymotrypsin. The arrow marks the position of the intact.

FIG. 7 shows the structure of (A) A beta 16-20m, (B) Anth-A beta 16-20m, (C) A beta 16-20, (D) A beta 16-22R, and (E) PrP115122m, all arrayed with a **beta-strand** conformation. In all of the **N** -**methylated** peptides depicted in the figure, the methyl groups would be aligned on one face of a **beta-strand**.

FIG. 8 shows electron microscopic examination of the effect of A beta 16-20 and A beta 16-20m on A beta 1-40 fibril formation. (A) Electron micrograph of A beta 1-40 incubated in the absence of inhibitor. Magnification, x 17,000. (B) Electron micrograph of A beta 1-40 incubated with a 20-fold molar excess of A beta 16-20m for seven days. Magnification, x 45,000. (C) Electron micrograph of A beta 1-40 incubated with a 20-fold molar excess of A beta 16-20 for seven days. Magnification, x 45,000. (D) Electron micrograph of A beta 16-20 added to A beta 1-40 fibrils which had been pre-formed by incubating A beta 1-40 for five days at 37 degrees C. Magnification x 45,000. (E) Electron micrograph of A beta 16-20 incubated in the absence of other peptides. Magnification x 45,000.

FIG. 9 shows inhibition and disassembly of A beta 40 fibrils by inhibitor peptides. (A) A beta 40 samples were incubated for one week at 37 degrees C. in the presence of various concentrations of peptides; thioflavin fluorescence was measured. In FIG. (B), the peptide inhibitors were added to A beta 40 fibrils which had been pre-formed by incubating A beta 40 for one week at 37 degrees C. After addition of peptide inhibitors, the mixtures were incubated for an additional three days at 37 C. After the incubation, a 10 mu l aliquot of peptide solution was diluted into 1 ml of 50 mM glycine, pH 8.5, containing 5 mu M thioflavin. Data are expressed as a percentage of the signal obtained in the absence of inhibitor peptides. The data are fit to an equation for a hyperbola parameters divided from nonlinear least squares analysis. Symbols are as follows: (circle-solid) A beta 16-20m; (*) A beta 16-20; (diamond-suit) AnthA beta 16-20m; (up-trianglefilled) A beta 16-22R.

FIG. 10 shows the rate of A beta 40 fibrils that had been preformed by incubating A beta 40 for one week at 37 degrees C. At the specified time points, a 5 mu l aliquot of each peptide solution was diluted into 1 mil of 50 mM glycine, pH 8.5, containing 5 mu M thioflavin. Data are expressed as a percentage of the signal obtained in the absence of inhibitor peptides. The data are fit to the equation for a first order rate process. Symbols are as follows: (circle-solid)A beta 1620m; A40 molar ratio, 5:1; A beta 16-20m:A beta 40 molar ratio, 10:1; (diamond-suit) A beta 16-20m:A beta 40 molar ratio, 20:1; (up-triangle-filled) A beta 16-20m:A beta beta 40 molar ratio, 30:1; (down-triangle-filled); A beta 16-20m:A beta 40 molar ratio, beta 40:1.

FIG. 11 shows inhibition of fibrillogenesis and disassembly of pre-formed fibrils is sequence specific. A beta 40 or Prp106126 was allowed to form fibrils. Each fibril-forming peptide was tested with A beta 16-20m or Prp115-112m. Extent of fibril formation or fibril disassemble was measured using a thioflavin fluorescence assay, as described herein. The X-axis is the ratio (mol:mol) of inhibitor peptide to fibril forming peptide for the various combinations; the Y-axis is the fluorescence expressed as a percentage of fluorescence obtained in the absence of inhibitor peptide. Lines are designated as representing either fibrillogenesis inhibition, or fibril disassembly. Symbols are as follows: (circle-solid) Prp115122 m+PrP106-126, Inhibition; (*) A beta 16-20 m+PrP106-126, Inhibition; (diamond-suit) A beta 16-20 m+PrP106-126, Disassembly; (up-triangle-filled) PrP115-122 m+A beta 40, Inhibition;

(down-triangle-filled) PrP115-122 m+A beta 40, Disassembly.

FIG. 12 shows (A) analytical ultracentrifugation sedimentation equilibrium of a 200 EM solution of A beta 16-20m in buffer (100 mM phosphate, 150 mM NaCl, pH 7.4) at 60,000 rpm. The data are displayed as normalized log plots. The solid lines drawn through the data were obtained by fitting the In (Absorbance) versus radius2 data to an equation of a single ideal species. Higher order fits resulted in poorer agreement with the experimental data. (B) The residual differences between the experimental data and theoretical curves are plotted in. (C) Size exclusion chromatography of an A beta 16-20m (1 mM) sample incubated at 37 degrees C. for one hour and (D) 72 hours. The column buffer was 100 mM phosphate buffer with 150 mM NaCl, pH 7.4. Absorbance was measured at 220 nm. The column volume is indicated by an arrow.

FIG. 13 shows circular dichroic spectra of A beta 16-20 and A beta 16-20m. (A) compares the spectra of A beta 16-20 (lambda) and A beta 16-20m (nu). The effects of (B) peptide concentration, (C) urea and (D) pH on the **beta-sheet** structure of A beta 16-20m, as reflected by the mean residue ellipticity at 226 nm, are displayed in the following panels. Data were collected as described in the experimental section.

FIG. 14 shows NMR spectroscopy of the A beta 16-20m peptide in phosphate buffer. (A) TOCSY spectra expanded in the H alpha proton region. Spin systems are identified by the single letter amino acid code and residue number. (B) ROESY spectra expanded in the H alpha proton region. Data were collected on a Varian 600 MHz instrument using presaturation for solvent suppression. Peaks were assigned using the TOCSY and DQF-COSY data.

FIG. 15 shows (A) efflux of (up-triangle-filled) 14C-A beta 1620m alone, (diamond-suit) 3H-glycine alone, and a mixture of 14C-A beta 16-20m (*) and 3H-glycine (circle-solid) from phosphotidylcholine vesicles. Phosphtidylcholine vesicles were prepared in the presence of 14C-labeled beta 16-20, 3H-glycine or a mixture of the two compounds. Free beta 16-20m and glycine were separated from the vesicles by passage over a G25 column (Pharmacia). The efflux of A beta 16-20m and glycine were measured using an ultrafiltration assay. Flux is expressed as a fraction of the total label; data were fit to a first-order rate equation. Efflux of calcein from phospotidylcholine vesicles. (B) different concentrations of A beta 16-20m (circle-solid) and A beta 16-20 (*) were incubated with phosphotidylcholine vesicles containing calcein for 3 hours at 37 degrees C. The fluorescence of the samples were then measured with an excitation wavelength of 490 nm and an emission wavelength of 520 nm. Data are expressed as a fraction of maximal fluorescence. (C) the rate of calcein efflux from phospotidylcholine vesicles was measured in the presence of beta 400 mu M A beta 16-20m. Fluorescence is expressed in arbitrary units. Data are fit to an equation for a first order rate process. (D) right angle light scattering of a vesicle solution in the presence (*) or absence (circle-solid) of A beta 16-20m. The turbidity of the solutions were measured by following the 90 degrees light scattering on a fluorescence spectrophotometer with both the excitation and emission wavelengths set to 600 nm. (E) and (F) Fluorescence data are expressed as arbitrary units. Fluorescence microscopy of COS cells incubated for twelve hours with 50 mu g of Anth beta 1620m. After the incubation period, the cells were washed, fixed with formaldehyde and examined by fluorescence microscopy using a DAPI filter.

FIG. 16 shows structures of (A) A beta 16-20m, (B) A beta 16-20 m2, (C) Anth-A beta 16-20m, (D) A beta 16-20, (E) A beta 16-20s and (F) PrP115-122m. All peptides are displayed in a betastrand conformation. In the N-methyl peptides shown in the FIG., the methyl groups are aligned on one hydrogen bonding face of the D-strand.

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FIG. 20 shows (A) Fluorescence microscopy of COS cells incubated for twelve hours with 40 mu M Anth-A beta 16-20m. After the incubation period, the cells were washed, fixed with formaldehyde and examined by fluorescence microscopy using a DAPI filter. (B) HPLC chromatogram of the Anth-A beta 16-20m peptide before incubation with COS cells. The elution gradient was from 0%-60% acetonitrile in 60 minutes. The peptide was detected by measuring the absorbance at 346 nm. (C) HPLC chromatogram of Anth-A beta 16-20m peptide that had been internalized by COS cells and then reisolated, as described in the Materials and Materials. The N-methyl anthranilic acidlabeled peptide was identified in the presence of other cellular peptides and proteins by fluorescence spectroscopy. The excitation and emission wavelengths were 346 nm and 435 nm, respectively. The HPLC gradient is the same as in (A).

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FIG. 24 shows how size exclusion chromatographs were obtained using a Superdex Peptide (Pharmacia) column. Peptide concentrations were 0.1, 0.2, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0 mg/ ml, as indicated. Chromatpographs are scaled so that, in each case, the largest peak is full scale. The data are consistent with the proposal that the ppetides undergo a reversible monomer-oligomer equilibrium. Both peaks eluted after the inclusion volume of the column as determined by the elution time of acetic acid and other low molecular weight markers). Although the recovery of the peptide from the column was virtually quantitative, the late elution of the peptides was consistent with adsorption of the peptide on all of the columns. For this reason, it was not possible to determine a molecular weight of the oligomer by this technique. Nevertheless, the concentration dependency of the aggregation could be analyzed using the following inferences. First, because the relative proportion of peptide in the earlier eluting peak increased with increasing concentration, we inferred that the earlier eluting peak was the oligomer. Second, since no other peaks were ever observed in any of the chromatograms, we inferred that the equilibrium could be analyzed as a simple case involving only two species. Third, because no peptide was observed to elute between the two peaks, and there was no "tailing" or either peak, we inferred that the equilibration was sufficiently slow that significant re-equilibration did not occur within the time frame of the chromatography. Using these inferences, the monomer-oligomer equilibrium was analyzed as described in the text.

FIG. 25 shows the mean residue ellipticity of A beta 16-22m and A beta 16-22mR were independent of peptide concentration. The graph shows the mean residue ellipticity at 226 nm as a function of total peptide concentration.

FIG. 26 shows structures of A beta 16-20 (A), A beta 16-20e (B) A beta 16-20m (C) PrP117-121 e (D) and (E) A beta 16-20-Bpa drawn with the peptide in beta-strand conformationss. In the ester and N-methyl peptides, the backbone modifications at alternating residues are aligned on one hydrogen bonding face of the beta-strand.

FIG. 27 ESI-MS detects non-covalent dimers of the A beta peptides. Shown are ESI-MS spectra of 250 mu M solutions of A beta 16-20e (A), A beta 16-20 (B) and A beta 16-20m (C). The samples were prepared in deionized water and the data were collected as described in the Materials and Methods section. The peaks corresponding to the monomer and dimer molecular weights for each peptide are labeled on the spectra.

FIG. 28 shows A beta 16-20-Bpa forms a covalent dimer upon irradiation with UV light. The MADI-MS spectrum of a 500 mu M solution of A beta 16-20 Bpa irradiated for 30 min at 350 nm shows peaks at 801.1 Da and 1600.8 Da, corresponding to monomeric and dimeric A 16-20-Bpa, respectively. The inset panel demosntrates that in the absence of irradiation, the dimer peak at 1600.8 Da is not observed in the MALDI-MS spectrum. !

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OTHER SOURCE(S): CASREACT 138:137570

AB **Amyloid** deposits are formed as a result of uncontrolled aggregation of (poly)peptides or proteins. Today several diseases are

known, for example Alzheimer's disease, Creutzfeldt-Jakob disease, mad cow disease, in which **amyloid** formation is involved. **Amyloid** fibrils are large aggregates of β-pleated sheets and here a general method is described to introduce mol. mutations in order to achieve disruption of β-sheet formation. Eight backbone-modified derivs. of amylin, an amyloidogenic peptide involved in maturity onset diabetes, were synthesized. Their β-sheet forming properties were studied by IR spectroscopy and electron microscopy. Modification of a crucial amide NH by an alkyl chain led to a complete loss of the β-sheet forming capacity of amylin. The resulting mol. mutated amylin derivative could be used to break the β-sheet thus retarding β-sheet formation of unmodified amylin. Moreover, it was found that the replacement of this amide bond by an ester moiety suppressed fibrillogenesis significantly. Introduction of **N-alkylated** amino acids and/or ester functionalities, leading to depsipeptides, into amyloidogenic peptides opens new avenues towards novel peptidic .**beta**.-**sheet** breakers for inhibition of β- **amyloid** aggregation.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 6 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 2002:27301 CAPLUS
DOCUMENT NUMBER: 136:307879
TITLE: Structure-based design and study of non-amyloidogenic, double N-methylated IAPP **amyloid** core sequences as inhibitors of IAPP **amyloid** formation and cytotoxicity
AUTHOR(S): Kapurniotu, Aphrodite; Schmauder, Anke; Tenidis, Konstantinos
CORPORATE SOURCE: Physiological-Chemical Institute, University of Tuebingen, Tuebingen, D-72076, Germany
SOURCE: Journal of Molecular Biology (2002), 315(3), 339-350
CODEN: JMOBAK; ISSN: 0022-2836
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Pancreatic **amyloid** is formed by the aggregation of the 37-residue islet **amyloid** polypeptide (IAPP) in type II diabetes patients and is cytotoxic. Pancreatic **amyloid** deposits are found in more than 95% of type II diabetes patients and their formation is strongly associated with disease progression. IAPP **amyloid** forms via a conformational transition of soluble IAPP into aggregated β-sheets. IAPP(22-27) (NFGAIL) was recently identified as a min. length sequence sufficient to self-associate into β-sheet-containing **amyloid** fibrils. Here, the NFGAIL model of the IAPP **amyloid** core was used as a structural template to design non-amyloidogenic derivs. of amyloidogenic sequences of IAPP that are able to interact with the native sequences and inhibit **amyloid** formation. The design of the derivs. was based on a simple, structure-based minimalistic and selective N-methylation approach. Accordingly, a min. number of two amide bonds on the same side of the .**beta**.-**strand** of the **amyloid** core was **N-methylated**. This was expected to eliminate the two intermol. backbone NH to CO hydrogen bonds which are critical for the extension of the β-sheet dimers into multimers and **amyloid**. Other β-strand "contact sides" remained intact allowing for the derivs. to interact with the native sequences. Double **N-methylated** derivs. of amyloidogenic and cytotoxic partial IAPP sequences generated included F(N-Me)GA(N-Me)IL, NF(N-Me)GA(N-Me)IL, SNNF(N-Me)GA(N-Me)IL, and SNNF(N-Me)GA(N-Me)ILSS and were found to be devoid of .**beta**.-**sheet** structure, amyloidogenicity and cytotoxicity according to Fourier transform-IR spectroscopy (FT-IR), Congo Red (CR) staining, electron microscopy (EM), and cell viability tests. The derivs. were able to interact with the native sequences and inhibit **amyloid** formation as shown by CD spectroscopy (CD), FT-IR and EM. Moreover, SNNF(N-Me)GA(N-Me)ILSS inhibited cytotoxicity of SNNFGAILSS and is thus the first reported inhibitor of IAPP **amyloid** formation and cytotoxicity. These results demonstrate the validity of the design

approach for IAPP and suggest that it may find application in understanding the structural features of **amyloid** formation and in the development of inhibitors of **amyloid** formation and cytotoxicity of other amyloidogenic polypeptides as well. (c) 2002 Academic Press.

REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 7 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 4

ACCESSION NUMBER: 2001:78415 CAPLUS
DOCUMENT NUMBER: 134:125971
TITLE: Peptides containing **N-substituted** D-amino acids for preventing .**beta**.-**strand** association
INVENTOR(S): Stott, Kelvin
PATENT ASSIGNEE(S): UK
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001007474	A1	20010201	WO 2000-GB2923	20000728
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2379241	AA	20010201	CA 2000-2379241	20000728
EP 1204679	A1	20020515	EP 2000-949729	20000728
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003505470	T2	20030212	JP 2001-512557	20000728
NZ 516442	A	20031031	NZ 2000-516442	20000728
AU 767396	B2	20031106	AU 2000-63004	20000728

PRIORITY APPLN. INFO.: GB 1999-17725 A 19990728
WO 2000-GB2923 W 20000728

AB Chemical compds. and compns. are disclosed which comprise peptides composed of D-enantiomers of amino acids and capable of binding to .**beta**.-**strand** structures to form .**beta**.-**sheets**, the peptides being selectively **N**α- **substituted** to prevent further .**beta**.-**strand** association The peptides are useful for preventing β-strand association The capacity of all-D-[Ac--Leu-MeLeu-Leu-MeLeu-Arg-Arg-NH2] to inhibit aggregation of a synthetic peptide fragment corresponding to residues 11-25 of the Alzheimer Aβ peptide into **amyloid** fibrils was determined

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 8 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 5

ACCESSION NUMBER: 2001:78414 CAPLUS
DOCUMENT NUMBER: 134:141772
TITLE: Peptides containing **N-substituted** L-amino acids for preventing .**beta**.-**strand** association
INVENTOR(S): Stott, Kelvin
PATENT ASSIGNEE(S): UK
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001007473	A1	20010201	WO 2000-GB2901	20000728
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2378779	AA	20010201	CA 2000-2378779	20000728
EP 1203019	A1	20020508	EP 2000-948175	20000728
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003505469	T2	20030212	JP 2001-512556	20000728
AU 766992	B2	20031030	AU 2000-61737	20000728
NZ 516441	A	20031128	NZ 2000-516441	20000728
PRIORITY APPLN. INFO.:			GB 1999-17724 A	19990728
			WO 2000-GB2901 W	20000728

AB Chemical compds. and compns. are disclosed which comprise peptides capable of binding to .**beta**.-**strand** structures to form . **beta**.-**sheets**, the peptides being selectively **N** α- **substituted** to prevent further .**beta**.-**strand** association The peptides are useful for preventing β-strand association The capacity of Ac-Arg-MeArg-Leu-MeLeu-Phe-MePhe-NH2 to inhibit aggregation of a synthetic peptide fragment corresponding to residues 11-25 of the Alzheimer Aβ peptide into **amyloid** fibrils was determined

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 9 OF 27 Elsevier BIOBASE COPYRIGHT 2005 Elsevier Science B.V. on STN

ACCESSION NUMBER: 1999197311 ESBIOBASE

TITLE: The aβ 3-pyroglutamyl and 11-pyroglutamyl peptides found in senile plaque have greater β-sheet forming and aggregation propensities in vitro than full-length Aβ

AUTHOR: He W.; Barrow C.J.

CORPORATE SOURCE: C.J. Barrow, School of Chemistry, University of Melbourne, Parkville, Vic. 3052, Australia. E-mail: c.barrow@chemistry.unimelb.edu.au

SOURCE: Biochemistry, (17 AUG 1999), 38/33 (10871-10877), 34 reference(s) CODEN: BICHAW ISSN: 0006-2960

DOCUMENT TYPE: Journal; Article

COUNTRY: United States

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Aβ isolated from neuritic plaque and vascular walls of the brains of patients with Alzheimer's disease has been shown to contain significant quantities of Aβ peptides which begin at residue .sup.3Glu or .sup.1.sup.1Glu in the form of pyroglutamyl residues (Aβ3pE and Aβ11pE). To investigate the effects of these **N**-terminal **modifications** on the biophysical properties of Aβ, peptides Aβ1-40, Aβ3pE-40, Aβ11pE40, Aβ1-28, Aβ3pE-28, and Aβ11pE- 28 were synthesized. Using circular dichroism spectroscopy, we determined that the pyroglutamyl-containing peptides form .**beta**.-**sheet** structure more readily than the corresponding full-length Aβ peptides, both in aqueous solutions and in 10% sodium dodecyl sulfate micelles. Trifluoroethanol spectra indicated that the relative .**beta**.-**sheet** to α-helical stability is higher for the pyroglutamyl-containing peptides. Sedimentation experiments show that the pyroglutamy-containing peptides have greater aggregation propensities than the corresponding

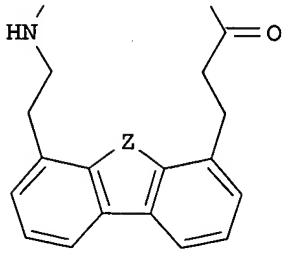
full-length peptides. Comparison between the Aβ40 and the Aβ28 series indicated that the greater .**beta.-sheet** forming and aggregation propensities of the pyroglutamyl peptides are not simply due to an increase in hydrophobicity.

L15 ANSWER 10 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:1468 CAPLUS
DOCUMENT NUMBER: 128:48506
TITLE: Preparation of diarylheterocycle derivatives as β-sheet nucleating peptidomimetics
INVENTOR(S): Kelly, Jeffrey W.
PATENT ASSIGNEE(S): Texas A & M University, USA
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9746547	A1	19971211	WO 1997-US9512	19970603
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 6034211	A	20000307	US 1996-664379	19960614
AU 9732954	A1	19980105	AU 1997-32954	19970603

PRIORITY APPLN. INFO.:
US 1996-18925P P 19960603
US 1996-664379 A 19960614
WO 1997-US9512 W 19970603

OTHER SOURCE(S): CASREACT 128:48506; MARPAT 128:48506
GI



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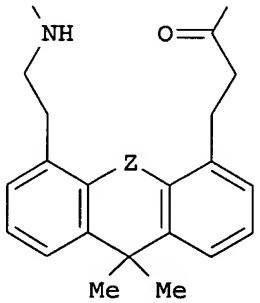

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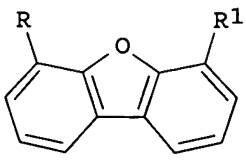

III

AB **N-methylated .beta.-sheet** nucleating peptidomimetics containing diarylheterocycle β-turn mimics I and II (Z = O, S, SO2, NRa, Ra = C1-6 alkyl), and methods of making and using them, are described. Thus, sequential lithiation and silylation of dibenzofuran gave mono-trimethylsilyl derivative III (R = H, R1 = SiMe3),

which underwent further lithiation and iodination to give iodo derivative III (R = iodo, R1 = SiMe3) in 75% yield after purification for both steps. Reaction of III (R = iodo, R1 = SiMe3) with Et acrylate in the presence of Pd(OAc)2 and tri-o-tolylphosphine gave 95% acrylate III (R = CH:CHCO2Et, R1 = SiMe3). Silyl derivative III (R = CH:CHCO2Et, R1 = SiMe3) was reacted with ICl to give the corresponding iodide, coupled with acrylic acid, and hydrogenated to give monoester III (R = CH2CH2CO2Et, R1 = CH2CH2CO2H) in 46% overall yield from dibenzofuran. The solid-phase preparation and conformational properties of a variety of 2-amino-3'-biphenylcarboxylate-containing peptides is also described. Peptidomimetics containing I and II are claimed to inhibit intramol. β-structure-dependent protein assembly, especially **amyloid** protein assembly.

L15 ANSWER 11 OF 27 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE
ACCESSION NUMBER: 1995:25227080 BIOTECHNO
TITLE: N-linked oligosaccharide of β- **amyloid** precursor protein (βAPP) of C6 glioma cells: Putative regulatory role in βAPP processing
AUTHOR: Saito F.; Tani A.; Miyatake T.; Yanagisawa K.
CORPORATE SOURCE: Department of Neuropathology, Institute for Brain Research, University of Tokyo, Hongo 7-3-1,Bunkyo-ku, Tokyo 113, Japan.
SOURCE: Biochemical and Biophysical Research Communications, (1995), 210/3 (703-710)
CODEN: BBRCA0 ISSN: 0006-291X
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1995:25227080 BIOTECHNO
AB To determine the **N-linked** oligosaccharide structure of β- **amyloid** precursor protein (βAPP), soluble derivative of βAPP (APPs) was purified from the conditioned medium of βAPP cDNA-transfected C6 glioma cells. Two types of APPs with different molecular weight (larger APPs, L-APPs; smaller APPs, S-APPs) were obtained. The antibody against the N-terminal half of **amyloid** β-protein showed no immunoreactivity with S-APPs, suggesting extensive truncation at the carboxyl terminus. From lectin blot analysis, the main structure of the **N-linked** oligosaccharide shared by L- and S-APPs was deduced to be of bi- or triantennary complex type with a fucosylated trimannosyl core and a bisecting GlcNAc residue. Additionally L-APPs was deduced to have Galβ1 → 4GlcNAc, Fucα1 → 2Galβ and Siaα2 → 6Gal. **beta. structures** on its outer chains. However, lectins which recognize Fucα1 → 2Galβ and Siaα2 → 6Gal. **beta. structures** showed no reactivity with S-APPs. The present results suggest that the processing of βAPP may be regulated via the heterogeneity in the fine structure of its sugar chains.

L15 ANSWER 12 OF 27 DGENE COPYRIGHT 2005 The Thomson Corp on STN
ACCESSION NUMBER: ABB82630 peptide DGENE
TITLE: Novel peptide for inhibiting fibrillogenesis, and for screening fibrillogenesis inhibitors, has beta-strand with one face having hydrogen bonds and other face blocking propagation of hydrogen bonding between beta-strands -
INVENTOR: Gordon D J; Meredith S C
PATENT ASSIGNEE: (UYCH-N)UNIV CHICAGO.
PATENT INFO: WO 2002074931 A2 20020926 151
APPLICATION INFO: WO 2002-US8803 20020320
PRIORITY INFO: US 2001-277477P 20010320
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-040553 [03]
DESCRIPTION: Abeta fibrillogenesis inhibitor peptide Abeta16-22.
AN ABB82630 peptide DGENE
AB The invention relates to a peptide (I) inhibiting fibrillogenesis, that comprises a **beta-strand** with two faces, where the

first face has hydrogen bonds, and the second face blocks or disrupts propagation of hydrogen bonding between **beta-strands** needed to form fibrils. (I) is useful for inhibiting fibrillogenesis, for detecting fibrils in a subject and for screening candidate fibrillogenesis inhibitors. A pharmaceutical composition comprising (I) is useful for inhibiting or disassembling fibrils associated with pathological states such as Alzheimer's disease, Down's syndrome, Dutch-Type hereditary cerebral haemorrhage amyloidosis, reactive amyloidosis, familial Mediterranean fever, familial **amyloid** nephropathy with utricaria and deafness, Muckle-Wells syndrome, idiopathic myeloma, macroglobulinemia-associated myeloma, familial **amyloid** polyneuropathy, familial **amyloid** cardiomyopathy, isolated cardiac **amyloid**, systemic senile amyloidosis, adult onset diabetes, insulinoma, isolated atrial **amyloid**, medullary carcinoma of the thyroid, familial amylodosis, hereditary cerebral haemorrhage with amyloidosis, familial amyloidotic polyneuropathy, scrapie, Creutzfeldt-Jakob disease, Gerstmann -Straussler-Scheinker syndrome, bovine spongiform encephalitis, prion-mediated diseases, or Huntington's disease. (I) is useful for treating disease associated with fibrillogenesis or for treating and/or diagnosing a subject which is a mammal, preferably human, having protein aggregation disease or protein misfolding disease. The composition is useful in both preventive and curative therapies of fibril based pathologies mentioned above. The present sequence represents a peptide which can comprise consecutive **N-methylation**, but is a weak inhibitor of Abeta fibrillogenesis.

L15 ANSWER 13 OF 27 DGENE COPYRIGHT 2005 The Thomson Corp on STN
ACCESSION NUMBER: AAW52997 peptide DGENE
TITLE: New **N-methylated beta-sheet** nucleating peptidomimetics - which contain di:aryl:heterocycle beta-turn mimics and may be used e.g. in treatment of amyloidosis
INVENTOR: Kelly J W
PATENT ASSIGNEE: (TEXA)UNIV TEXAS A & M SYSTEM.
PATENT INFO: WO 9746547 A1 19971211 74
APPLICATION INFO: WO 1997-US9512 19970603
PRIORITY INFO: US 1996-664379 19960614
US 1996-18925 19960603
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1998-042098 [04]
DESCRIPTION: **N-methylated beta-sheet** nucleating peptidometic 6.
AN AAW52997 peptide DGENE
AB The new beta-sheet nucleating peptidomimetics (AAW52992-W53006) comprise a diarylheterocycle, a recognition strand of 3-21 amino acid residues and a blocking strand of 3-21 amino acid residues. The peptidomimetics inhibit intermolecular aggregation and can be used as therapeutic agents for diseases that are mediated by a protein which requires assembly, such as self-assembly of dimeric or oligomeric forms, for activity (e.g. enzymatic activity). They may be used to inhibit **amyloid** protein assembly and thus to treat cross- beta **amyloid** fibril-mediated diseases, such as Alzheimer's disease. They may also be used for down-regulating target peptides (such as somatostatin) and for imaging of target proteins.

L15 ANSWER 14 OF 27 DGENE COPYRIGHT 2005 The Thomson Corp on STN
ACCESSION NUMBER: AAW52996 peptide DGENE
TITLE: New **N-methylated beta-sheet** nucleating peptidomimetics - which contain di:aryl:heterocycle beta-turn mimics and may be used e.g. in treatment of amyloidosis
INVENTOR: Kelly J W
PATENT ASSIGNEE: (TEXA)UNIV TEXAS A & M SYSTEM.
PATENT INFO: WO 9746547 A1 19971211 74
APPLICATION INFO: WO 1997-US9512 19970603
PRIORITY INFO: US 1996-664379 19960614
US 1996-18925 19960603

DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1998-042098 [04]
DESCRIPTION: **N-methylated beta-sheet** nucleating peptidometic 5.

AN AAW52996 peptide DGENE
AB The new beta-sheet nucleating peptidomimetics (AAW52992-W53006) comprise a diarylheterocycle, a recognition strand of 3-21 amino acid residues and a blocking strand of 3-21 amino acid residues. The peptidomimetics inhibit intermolecular aggregation and can be used as therapeutic agents for diseases that are mediated by a protein which requires assembly, such as self-assembly of dimeric or oligomeric forms, for activity (e.g. enzymatic activity). They may be used to inhibit **amyloid** protein assembly and thus to treat cross- beta **amyloid** fibril-mediated diseases, such as Alzheimer's disease. They may also be used for down-regulating target peptides (such as somatostatin) and for imaging of target proteins.

L15 ANSWER 15 OF 27 DGENE COPYRIGHT 2005 The Thomson Corp on STN
ACCESSION NUMBER: AAW52995 peptide DGENE
TITLE: New **N-methylated beta-sheet** nucleating peptidomimetics - which contain di:aryl:heterocycle beta-turn mimics and may be used e.g. in treatment of amyloidosis
INVENTOR: Kelly J W
PATENT ASSIGNEE: (TEXA)UNIV TEXAS A & M SYSTEM.
PATENT INFO: WO 9746547 A1 19971211 74
APPLICATION INFO: WO 1997-US9512 19970603
PRIORITY INFO: US 1996-664379 19960614
US 1996-18925 19960603
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1998-042098 [04]
DESCRIPTION: **N-methylated beta-sheet** nucleating peptidometic 4.

AN AAW52995 peptide DGENE
AB The new beta-sheet nucleating peptidomimetics (AAW52992-W53006) comprise a diarylheterocycle, a recognition strand of 3-21 amino acid residues and a blocking strand of 3-21 amino acid residues. The peptidomimetics inhibit intermolecular aggregation and can be used as therapeutic agents for diseases that are mediated by a protein which requires assembly, such as self-assembly of dimeric or oligomeric forms, for activity (e.g. enzymatic activity). They may be used to inhibit **amyloid** protein assembly and thus to treat cross- beta **amyloid** fibril-mediated diseases, such as Alzheimer's disease. They may also be used for down-regulating target peptides (such as somatostatin) and for imaging of target proteins.

L15 ANSWER 16 OF 27 DGENE COPYRIGHT 2005 The Thomson Corp on STN
ACCESSION NUMBER: AAW52994 peptide DGENE
TITLE: New **N-methylated beta-sheet** nucleating peptidomimetics - which contain di:aryl:heterocycle beta-turn mimics and may be used e.g. in treatment of amyloidosis
INVENTOR: Kelly J W
PATENT ASSIGNEE: (TEXA)UNIV TEXAS A & M SYSTEM.
PATENT INFO: WO 9746547 A1 19971211 74
APPLICATION INFO: WO 1997-US9512 19970603
PRIORITY INFO: US 1996-664379 19960614
US 1996-18925 19960603
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1998-042098 [04]
DESCRIPTION: **N-methylated beta-sheet** nucleating peptidometic 3.

AN AAW52994 peptide DGENE
AB The new beta-sheet nucleating peptidomimetics (AAW52992-W53006) comprise a diarylheterocycle, a recognition strand of 3-21 amino acid residues and a blocking strand of 3-21 amino acid residues. The peptidomimetics

inhibit intermolecular aggregation and can be used as therapeutic agents for diseases that are mediated by a protein which requires assembly, such as self-assembly of dimeric or oligomeric forms, for activity (e.g. enzymatic activity). They may be used to inhibit **amyloid** protein assembly and thus to treat cross- beta **amyloid** fibril-mediated diseases, such as Alzheimer's disease. They may also be used for down-regulating target peptides (such as somatostatin) and for imaging of target proteins.

L15 ANSWER 17 OF 27 DGENE COPYRIGHT 2005 The Thomson Corp on STN
ACCESSION NUMBER: AAW52992 peptide DGENE
TITLE: New **N-methylated beta-sheet** nucleating peptidomimetics - which contain di:aryl:heterocycle beta-turn mimics and may be used e.g. in treatment of amyloidosis
INVENTOR: Kelly J W
PATENT ASSIGNEE: (TEXA)UNIV TEXAS A & M SYSTEM.
PATENT INFO: WO 9746547 A1 19971211 74
APPLICATION INFO: WO 1997-US9512 19970603
PRIORITY INFO: US 1996-664379 19960614
US 1996-18925 19960603
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1998-042098 [04]
DESCRIPTION: **N-methylated beta-sheet** nucleating peptidometic 1.
AN AAW52992 peptide DGENE
AB The new beta-sheet nucleating peptidomimetics (AAW52992-W53006) comprise a diarylheterocycle, a recognition strand of 3-21 amino acid residues and a blocking strand of 3-21 amino acid residues. The peptidomimetics inhibit intermolecular aggregation and can be used as therapeutic agents for diseases that are mediated by a protein which requires assembly, such as self-assembly of dimeric or oligomeric forms, for activity (e.g. enzymatic activity). They may be used to inhibit **amyloid** protein assembly and thus to treat cross- beta **amyloid** fibril-mediated diseases, such as Alzheimer's disease. They may also be used for down-regulating target peptides (such as somatostatin) and for imaging of target proteins.

L15 ANSWER 18 OF 27 DGENE COPYRIGHT 2005 The Thomson Corp on STN
ACCESSION NUMBER: AAW52993 peptide DGENE
TITLE: New **N-methylated beta-sheet** nucleating peptidomimetics - which contain di:aryl:heterocycle beta-turn mimics and may be used e.g. in treatment of amyloidosis
INVENTOR: Kelly J W
PATENT ASSIGNEE: (TEXA)UNIV TEXAS A & M SYSTEM.
PATENT INFO: WO 9746547 A1 19971211 74
APPLICATION INFO: WO 1997-US9512 19970603
PRIORITY INFO: US 1996-664379 19960614
US 1996-18925 19960603
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1998-042098 [04]
DESCRIPTION: **N-methylated beta-sheet** nucleating peptidometic 2.
AN AAW52993 peptide DGENE
AB The new beta-sheet nucleating peptidomimetics (AAW52992-W53006) comprise a diarylheterocycle, a recognition strand of 3-21 amino acid residues and a blocking strand of 3-21 amino acid residues. The peptidomimetics inhibit intermolecular aggregation and can be used as therapeutic agents for diseases that are mediated by a protein which requires assembly, such as self-assembly of dimeric or oligomeric forms, for activity (e.g. enzymatic activity). They may be used to inhibit **amyloid** protein assembly and thus to treat cross- beta **amyloid** fibril-mediated diseases, such as Alzheimer's disease. They may also be used for down-regulating target peptides (such as somatostatin) and for imaging of target proteins.

L15 ANSWER 19 OF 27 DGENE COPYRIGHT 2005 The Thomson Corp on STN
ACCESSION NUMBER: AAW52999 peptide DGENE
TITLE: New **N-methylated beta-sheet** nucleating peptidomimetics - which contain di:aryl:heterocycle beta-turn mimics and may be used e.g. in treatment of amyloidosis
INVENTOR: Kelly J W
PATENT ASSIGNEE: (TEXA)UNIV TEXAS A & M SYSTEM.
PATENT INFO: WO 9746547 A1 19971211 74
APPLICATION INFO: WO 1997-US9512 19970603
PRIORITY INFO: US 1996-664379 19960614
US 1996-18925 19960603
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1998-042098 [04]
DESCRIPTION: **N-methylated beta-sheet** nucleating peptidometic 8.
AN AAW52999 peptide DGENE
AB The new beta-sheet nucleating peptidomimetics (AAW52992-W53006) comprise a diarylheterocycle, a recognition strand of 3-21 amino acid residues and a blocking strand of 3-21 amino acid residues. The peptidomimetics inhibit intermolecular aggregation and can be used as therapeutic agents for diseases that are mediated by a protein which requires assembly, such as self-assembly of dimeric or oligomeric forms, for activity (e.g. enzymatic activity). They may be used to inhibit **amyloid** protein assembly and thus to treat cross- beta **amyloid** fibril-mediated diseases, such as Alzheimer's disease. They may also be used for down-regulating target peptides (such as somatostatin) and for imaging of target proteins.

L15 ANSWER 20 OF 27 DGENE COPYRIGHT 2005 The Thomson Corp on STN
ACCESSION NUMBER: AAW52998 peptide DGENE
TITLE: New **N-methylated beta-sheet** nucleating peptidomimetics - which contain di:aryl:heterocycle beta-turn mimics and may be used e.g. in treatment of amyloidosis
INVENTOR: Kelly J W
PATENT ASSIGNEE: (TEXA)UNIV TEXAS A & M SYSTEM.
PATENT INFO: WO 9746547 A1 19971211 74
APPLICATION INFO: WO 1997-US9512 19970603
PRIORITY INFO: US 1996-664379 19960614
US 1996-18925 19960603
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1998-042098 [04]
DESCRIPTION: **N-methylated beta-sheet** nucleating peptidometic 7.
AN AAW52998 peptide DGENE
AB The new beta-sheet nucleating peptidomimetics (AAW52992-W53006) comprise a diarylheterocycle, a recognition strand of 3-21 amino acid residues and a blocking strand of 3-21 amino acid residues. The peptidomimetics inhibit intermolecular aggregation and can be used as therapeutic agents for diseases that are mediated by a protein which requires assembly, such as self-assembly of dimeric or oligomeric forms, for activity (e.g. enzymatic activity). They may be used to inhibit **amyloid** protein assembly and thus to treat cross- beta **amyloid** fibril-mediated diseases, such as Alzheimer's disease. They may also be used for down-regulating target peptides (such as somatostatin) and for imaging of target proteins.

L15 ANSWER 21 OF 27 DGENE COPYRIGHT 2005 The Thomson Corp on STN
ACCESSION NUMBER: AAW53006 peptide DGENE
TITLE: New **N-methylated beta-sheet** nucleating peptidomimetics - which contain di:aryl:heterocycle beta-turn mimics and may be used e.g. in treatment of amyloidosis
INVENTOR: Kelly J W
PATENT ASSIGNEE: (TEXA)UNIV TEXAS A & M SYSTEM.
PATENT INFO: WO 9746547 A1 19971211 74

APPLICATION INFO: WO 1997-US9512 19970603
PRIORITY INFO: US 1996-664379 19960614
US 1996-18925 19960603
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1998-042098 [04]
DESCRIPTION: **N-methylated beta-sheet** nucleating peptidometic 15.

AN AAW53006 peptide DGENE
AB The new beta-sheet nucleating peptidomimetics (AAW52992-W53006) comprise a diarylheterocycle, a recognition strand of 3-21 amino acid residues and a blocking strand of 3-21 amino acid residues. The peptidomimetics inhibit intermolecular aggregation and can be used as therapeutic agents for diseases that are mediated by a protein which requires assembly, such as self-assembly of dimeric or oligomeric forms, for activity (e.g. enzymatic activity). They may be used to inhibit **amyloid** protein assembly and thus to treat cross- beta **amyloid** fibril-mediated diseases, such as Alzheimer's disease. They may also be used for down-regulating target peptides (such as somatostatin) and for imaging of target proteins.

L15 ANSWER 22 OF 27 DGENE COPYRIGHT 2005 The Thomson Corp on STN
ACCESSION NUMBER: AAW53005 peptide DGENE
TITLE: New **N-methylated beta-sheet** nucleating peptidomimetics - which contain di:aryl:heterocycle beta-turn mimics and may be used e.g. in treatment of amyloidosis
INVENTOR: Kelly J W
PATENT ASSIGNEE: (TEXA)UNIV TEXAS A & M SYSTEM.
PATENT INFO: WO 9746547 A1 19971211 74
APPLICATION INFO: WO 1997-US9512 19970603
PRIORITY INFO: US 1996-664379 19960614
US 1996-18925 19960603
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1998-042098 [04]
DESCRIPTION: **N-methylated beta-sheet** nucleating peptidometic 14.

AN AAW53005 peptide DGENE
AB The new beta-sheet nucleating peptidomimetics (AAW52992-W53006) comprise a diarylheterocycle, a recognition strand of 3-21 amino acid residues and a blocking strand of 3-21 amino acid residues. The peptidomimetics inhibit intermolecular aggregation and can be used as therapeutic agents for diseases that are mediated by a protein which requires assembly, such as self-assembly of dimeric or oligomeric forms, for activity (e.g. enzymatic activity). They may be used to inhibit **amyloid** protein assembly and thus to treat cross- beta **amyloid** fibril-mediated diseases, such as Alzheimer's disease. They may also be used for down-regulating target peptides (such as somatostatin) and for imaging of target proteins.

L15 ANSWER 23 OF 27 DGENE COPYRIGHT 2005 The Thomson Corp on STN
ACCESSION NUMBER: AAW53004 peptide DGENE
TITLE: New **N-methylated beta-sheet** nucleating peptidomimetics - which contain di:aryl:heterocycle beta-turn mimics and may be used e.g. in treatment of amyloidosis
INVENTOR: Kelly J W
PATENT ASSIGNEE: (TEXA)UNIV TEXAS A & M SYSTEM.
PATENT INFO: WO 9746547 A1 19971211 74
APPLICATION INFO: WO 1997-US9512 19970603
PRIORITY INFO: US 1996-664379 19960614
US 1996-18925 19960603
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1998-042098 [04]
DESCRIPTION: **N-methylated beta-sheet** nucleating peptidometic 13.

AN AAW53004 peptide DGENE

AB The new beta-sheet nucleating peptidomimetics (AAW52992-W53006) comprise a diarylheterocycle, a recognition strand of 3-21 amino acid residues and a blocking strand of 3-21 amino acid residues. The peptidomimetics inhibit intermolecular aggregation and can be used as therapeutic agents for diseases that are mediated by a protein which requires assembly, such as self-assembly of dimeric or oligomeric forms, for activity (e.g. enzymatic activity). They may be used to inhibit **amyloid** protein assembly and thus to treat cross- beta **amyloid** fibril-mediated diseases, such as Alzheimer's disease. They may also be used for down-regulating target peptides (such as somatostatin) and for imaging of target proteins.

L15 ANSWER 24 OF 27 DGENE COPYRIGHT 2005 The Thomson Corp on STN
ACCESSION NUMBER: AAW53003 peptide DGENE
TITLE: New **N-methylated beta-sheet** nucleating peptidomimetics - which contain di:aryl:heterocycle beta-turn mimics and may be used e.g. in treatment of amyloidosis
INVENTOR: Kelly J W
PATENT ASSIGNEE: (TEXA)UNIV TEXAS A & M SYSTEM.
PATENT INFO: WO 9746547 A1 19971211 74
APPLICATION INFO: WO 1997-US9512 19970603
PRIORITY INFO: US 1996-664379 19960614
US 1996-18925 19960603
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1998-042098 [04]
DESCRIPTION: **N-methylated beta-sheet** nucleating peptidometic 12.
AN AAW53003 peptide DGENE
AB The new beta-sheet nucleating peptidomimetics (AAW52992-W53006) comprise a diarylheterocycle, a recognition strand of 3-21 amino acid residues and a blocking strand of 3-21 amino acid residues. The peptidomimetics inhibit intermolecular aggregation and can be used as therapeutic agents for diseases that are mediated by a protein which requires assembly, such as self-assembly of dimeric or oligomeric forms, for activity (e.g. enzymatic activity). They may be used to inhibit **amyloid** protein assembly and thus to treat cross- beta **amyloid** fibril-mediated diseases, such as Alzheimer's disease. They may also be used for down-regulating target peptides (such as somatostatin) and for imaging of target proteins.

L15 ANSWER 25 OF 27 DGENE COPYRIGHT 2005 The Thomson Corp on STN
ACCESSION NUMBER: AAW53002 peptide DGENE
TITLE: New **N-methylated beta-sheet** nucleating peptidomimetics - which contain di:aryl:heterocycle beta-turn mimics and may be used e.g. in treatment of amyloidosis
INVENTOR: Kelly J W
PATENT ASSIGNEE: (TEXA)UNIV TEXAS A & M SYSTEM.
PATENT INFO: WO 9746547 A1 19971211 74
APPLICATION INFO: WO 1997-US9512 19970603
PRIORITY INFO: US 1996-664379 19960614
US 1996-18925 19960603
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1998-042098 [04]
DESCRIPTION: **N-methylated beta-sheet** nucleating peptidometic 11.
AN AAW53002 peptide DGENE
AB The new beta-sheet nucleating peptidomimetics (AAW52992-W53006) comprise a diarylheterocycle, a recognition strand of 3-21 amino acid residues and a blocking strand of 3-21 amino acid residues. The peptidomimetics inhibit intermolecular aggregation and can be used as therapeutic agents for diseases that are mediated by a protein which requires assembly, such as self-assembly of dimeric or oligomeric forms, for activity (e.g. enzymatic activity). They may be used to inhibit **amyloid** protein assembly and thus to treat cross- beta **amyloid** fibril-mediated diseases, such as Alzheimer's disease. They may also be

used for down-regulating target peptides (such as somatostatin) and for imaging of target proteins.

L15 ANSWER 26 OF 27 DGENE COPYRIGHT 2005 The Thomson Corp on STN
ACCESSION NUMBER: AAW53001 peptide DGENE
TITLE: New **N-methylated beta-sheet** nucleating peptidomimetics - which contain di:aryl:heterocycle beta-turn mimics and may be used e.g. in treatment of amyloidosis
INVENTOR: Kelly J W
PATENT ASSIGNEE: (TEXA)UNIV TEXAS A & M SYSTEM.
PATENT INFO: WO 9746547 A1 19971211 74
APPLICATION INFO: WO 1997-US9512 19970603
PRIORITY INFO: US 1996-664379 19960614
US 1996-18925 19960603
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1998-042098 [04]
DESCRIPTION: **N-methylated beta-sheet** nucleating peptidometic 10.
AN AAW53001 peptide DGENE
AB The new beta-sheet nucleating peptidomimetics (AAW52992-W53006) comprise a diarylheterocycle, a recognition strand of 3-21 amino acid residues and a blocking strand of 3-21 amino acid residues. The peptidomimetics inhibit intermolecular aggregation and can be used as therapeutic agents for diseases that are mediated by a protein which requires assembly, such as self-assembly of dimeric or oligomeric forms, for activity (e.g. enzymatic activity). They may be used to inhibit **amyloid** protein assembly and thus to treat cross- beta **amyloid** fibril-mediated diseases, such as Alzheimer's disease. They may also be used for down-regulating target peptides (such as somatostatin) and for imaging of target proteins.

L15 ANSWER 27 OF 27 DGENE COPYRIGHT 2005 The Thomson Corp on STN
ACCESSION NUMBER: AAW53000 peptide DGENE
TITLE: New **N-methylated beta-sheet** nucleating peptidomimetics - which contain di:aryl:heterocycle beta-turn mimics and may be used e.g. in treatment of amyloidosis
INVENTOR: Kelly J W
PATENT ASSIGNEE: (TEXA)UNIV TEXAS A & M SYSTEM.
PATENT INFO: WO 9746547 A1 19971211 74
APPLICATION INFO: WO 1997-US9512 19970603
PRIORITY INFO: US 1996-664379 19960614
US 1996-18925 19960603
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1998-042098 [04]
DESCRIPTION: **N-methylated beta-sheet** nucleating peptidometic 9.
AN AAW53000 peptide DGENE
AB The new beta-sheet nucleating peptidomimetics (AAW52992-W53006) comprise a diarylheterocycle, a recognition strand of 3-21 amino acid residues and a blocking strand of 3-21 amino acid residues. The peptidomimetics inhibit intermolecular aggregation and can be used as therapeutic agents for diseases that are mediated by a protein which requires assembly, such as self-assembly of dimeric or oligomeric forms, for activity (e.g. enzymatic activity). They may be used to inhibit **amyloid** protein assembly and thus to treat cross- beta **amyloid** fibril-mediated diseases, such as Alzheimer's disease. They may also be used for down-regulating target peptides (such as somatostatin) and for imaging of target proteins.

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